Experimental Constriction of Thoracic Inferior Vena Cava in Dogs : Histopathological Changes in Lungs, Factors Contributing to Pulmonary Edema

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Experimental Constriction of Thoracic Inferior Vena Cava in Dogs

(Histopathological Changes in Lungs, Factors Contributing to Pulmonary Edema)

by

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In Japan a total of 119 cases of complete or partial obstruction of the hepatic veins and/or the corresponding portion of the inferior vena cava have been reported[1]. Out of 33 autopsies performed 16 demonstrated finding of pulmonary edema. Although many investigators[2)-15)] reported passive liver congestion and ascites, few descrived pulmonary edema in experimental animals following constriction of the thoracic inferior vena cava.

The aim of this paper is to present histopathological changes in the lungs of dogs whose inferior vena cava was constricted and to elucidate the mechanism by which it is produced.

MATERIAL AND METHODS

Adult mongrel dogs, 7 to 19 kg, were used in this study. Anesthesia for the operative procedures was provided through the use of nembutal intravenously in doses of about 30 mg per kg of body weight. An endotracheal tube was inserted.

Surgical Procedures: An incision following the curve of the right sixth intercostal space anteriorly was made. The pleural cavity was entered, and the sixth and seventh ribs were drawn apart and fixed by a self-retaining retractor, exposing the thoracic portion of the inferior vena cava. The right phrenic nerve was then dissected free for a distance of about 2 cm and the thoracic portion of the inferior vena cava was constricted by ligature to about one-half of its normal diameter. The lungs were then inflated, and the two ribs were brought together with silk sutures.

Pathological Studies: Organspecimens were fixed in formalin and stained with hematoxylin and eosin.

Main Pulmonary Artery Pressure and Pulmonary Artery Wedge Pressure: These pressures were obtained using a radio-opaque cardiac catheter connected to electric manometer and recorded. A longitudinal incision about 3 cm in length was made under nembutal anesthesia. The right external juglar vein was isolated, and the catheter tip was inserted into the vein and advanced under fluoroscopic control.

Determination of Serum and Ascitic Fluid Proteins: The protein content was determined with a refractometer. Cellulose acetate electrophoresis was used for fractionation of proteins, and the strips were stained with Ponceau 3 R[16)17)]. The density of dye was measured photometrically.

Determiniation of the Electrolytes Levels: A Baird flame photometer was used to

determine potassium and sodium levels in serum and ascitic fluid. Chlorides in serum and ascites were determined by the method of Schales & Schales.

The protein content and potassium level of serum obtained from anesthetized dog were always lower than those of serum from the same dog before administering nembutal intravenously. Therefore, blood and ascitic fluid samples for proteins and electrolytes analyses were collected from non-anesthetized dogs.

The rate of fluid uptake from the lung was measured with the radioisotope, P^{32}: Dogs were anesthetized with about 30 mg of nembutal per kg of body weight. If necessary, additional doses were added during the experiment. A tracheal catheter was then inserted. The femoral artery was exposed through a small incision in the groin and cannulated with polyethylene tubing for collection of blood samples. Ascites samples were taken by abdominal paracentesis. 0.5 cc of P^{32} in physiological salt solution (1 mc/cc) was added to the solution of 1.5 cc of 0.5 % T 1824 and was introduced into the lung through a polyethylene tubing inserted into a tracheal catheter. To prevent loss of fluid the head of the dog was elevated at about 20° angle. Blood and ascitic fluid samples were collected in small heparinised glass ampules at different time intervals. Determination of the radioactivity of 0.2 cc of each of the samples was made by a automatic gas-flow counter.

RESULTS

1) Macro and Microscopic Findings of the Lungs: Twenty-nine dogs were used in this study. One died 2 hours and the remaining 21 survived up to 520 days after the operation. Seven were sacrificed by intravenous administration of nembutal between the 8 th and 182 nd days postoperatively. Ten dogs died within 4 days after operation. In 7 of these 10 animals, the lungs showed congestion but no edema on gross examination. In the remaining 3, macro and microscopic examination revealed pulmonary edema. All of 12 dogs which died between the 14 th and 521 st days after constriction showed a moderate to severe degree of pulmonary edema. In 5 of 7 dogs which were sacrificed, there was no clinical evidence of pulmonary edema. In 1 of these 5, microscopic examination showed a severe pulmonary edema. In the remaining 2 which survived 32 and 33 days respectively, a clinically severe pulmonary edema developed on the day when they were sacrificed. Typical examples are presented.

Dog No. 51 which remained asymptomatic except ascites for 120 days after operation was sacrificed by the intravenous administration of a large dose of nembutal. At autopsy, no fluid was found in pleural cavities. On gross examination the lungs appeared normal. Microscopic examination revealed only slightly congested blood vessels. There was no inflammatory lesion. The alveolar partitions were slightly thickened in some regions. There was no dilatation of peribronchial or perivascular lymphatics.

Dog No. 28 died on the 84 th postoperative day. At autopsy, the right pleural cavity contained 10 cc of serosanguinous fluid and the left 5 cc. The pericardial sack contained 5 cc of a straw colored fluid. A severe degree of pulmonary edema was evident on microscopic examination. There was no inflammatory lesion. Sections taken out of the right upper lobe showed exudate in the proximity of the blood vessels (figure 13).

Dog No. 37 which was sacrificed on the 20 th postoperative day did not have pleural effusion. There was a great amount of transudate in the alveoli and in the bronchi (figure 14). The perivascular lymphatics were filled with fluid (figure 15). Inflammatory lesion was not found.

Dog No. 32 was severely dyspneic and cyanotic and developed acute pulmonary edema, with continuous emission of copious amounts of pink, frothy fluid from the nose on the 33 rd postoperative day. The dog was sacrificed and autopsy performed. Left pleural sack contained 200 cc of serosanguinous fluid. Right pleural sac contained 100 cc of fluid of similar appearance. On section the cut surfaces of the lungs were wet and many small and large bronchi exuded frothy hemorrhagic fluid, as did the trachea. On microscopic examination, sections taken from the left lower and right upper lobes showed a large amount of intra-alveolar transudate, many red cells, macrophages and moderate numbers of leucocytes (figure 16). The dilatation of perivascular and peribronchial lymph vessels was not observed. Sections of the right lower lobe showed thickning of alveolar walls and the alveoli and bronchioles frequently contained a few red cells and macrophages. There was no visible transudate in the alveoli and in the bronchi.

2) Pulmonary artery wedge pressure and main pulmonary artery pressure were obtained in 8 normal dogs and in 6 dogs in which supradiaphragmatic constriction of the inferior vena cava had been performed 19 to 106 days previously. The data are reported in table 1. Normal P. A. Wedge P. was between 7 and 13 mmHg and normal main P. A. P. was between 17 and 39 (systolic), between 13 and 26.5 (diastolic). In 5 of 6 dogs with vena cava constriction P. A. Wedge P. was between 6.5 and 12, and in 1 20 mmHg. In 5 of these 6 dogs systolic main P. A. P. was between 15 and 35, and in 1 44 mmHg.

3) The normal values for total serum proteins were between 6.1 and 8.8 gm per 100 ml, with an average of 7.4 gm (table 2). With cellulose acetate electrophoresis, the concentration of serum albumin ranged from 2.82 to 4.27 gm per 100 ml serum. The

Table 1 Pulmonary Artery Wedge and Main Pulmonary Artery Pressures (mmHg)

Dog No.	Normal Dogs			Dogs with Constriction of Thoracic Inferior Vena Cava			Ascitic Fluid
	Pulmonary Artery Wedge Pressure	Pulmonary Artery Pressure		Pulmonary Artery Wedge Pressure	Pulmonary Artery Pressure		
		Systolic	Diastolic		Systolic	Diastolic	
27	9	33	20	8.5	15	9	##
28	9	39	26.5	8.5	44	38	##
35	13	24.5	16	20	35	25	##
20				6.5	22.5	16.5	#
25				7	20	14	##
21				12	25.5	20.5	+
29	8.5	26	15				
30	9	28.5	13				
31	10	17	13.5				
33	8.5	20	15				
34	7	30	26				

Table 2 Normal Levels of Serum Proteins in Dogs (gm per 100 ml serum)

	Total protein	Albumin	Globulin	A/G ratio
1	7.3	3.35	3.95	0.85
2	8.8	3.54	5.26	0.67
3	6.5	3.38	3.12	1.08
4	7.8	3.28	4.52	0.73
5	8.1	3.82	4.28	0.89
6	6.8	3.50	3.30	1.06
7	7.6	4.09	3.51	1.16
8	8.0	4.27	3.73	1.14
9	6.1	2.82	3.28	0.86
10	6.5	3.58	2.92	1.23
11	6.9	3.55	3.35	1.06
12	7.2	3.25	3.95	0.83
13	6.8	3.25	3.55	0.92
14	8.6	2.91	5.69	0.51
15	7.9	3.04	4.86	0.63
16	7.1	3.71	3.39	1.09
17	7.8	3.42	4.38	0.78
18	7.4	3.86	3.54	1.09
19	6.9	2.84	4.06	0.70
20	6.9	3.45	3.45	1.00
Mean	7.4	3.45	3.90	0.91

concentration of serum globulin ranged from 2.92 to 5.69 gm per 100 ml serum.

Total serum protein and serum albumin levels were reduced promptly after inferior vena caval constriction.

In dog No. 55 (figure 1), the presence of intraperitoneal fluid was verified by abdominal paracentesis on the 5 th postoperative day, and the ascites was irreversible and persisted until the death of the dog on the 63 rd postoperative day. In this dog total serum protein concentration fell from 8.0 to 3.9 gm per 100 ml serum 12 days after partial ligation of the inferior vena cava and then began to increase gradually, but remained below normal value. Serum albumin and globulin levels also fell from 4.3 and 3.7 to 1.6 and 2.3 gm per 100 ml serum respectively. The A/G ratios were lower. The values for total ascitic fluid proteins, albumin and globulin ran parallel to those of the serum.

In dog No. 52 (figure 2), the presence of gradually increasing ascitic fluid was detected 5 days after operation. About two weeks later, the amount of ascitic fluid began to decrease and 26 days after operation no fluid was found. In this dog total serum protein concentration fell from 6.9 to 4.3 gm seven days after operation and recovered to normal concentration sixteen days after constriction. Serum albumin level also fell from 3.5 to 1.4 gm per 100 ml serum and recovered to normal values 47 days after constriction. The values for total ascitic fluid protein, albumin and globulin showed similar pattern to those of the serum.

In dog No. 59 (figure 3), no ascitic fluid was found during the postoperative course, but the total serum protein, albumin and globulin decreased immediately after constriction.

In another 2 dogs (No. 51 and 57) with ascitic fluid, the similar patterns were seen (figures 4 and 5).

Six dogs were used in this study and ascitic fluid was found in all but one (dog No. 59).

4) Changes in electrolytes levels of serum and ascitic fluid are shown in figures 6-11. In 5 dogs on normal diet serum sodium levels decreased for a few days after constriction, then increased (figures 6-10). One dog on high sodium intake, showed gradual increase of serum sodium levels (figure 11). The values for serum potassium were higher than those of the ascites. Even when ascitic fluid formation was markedly increased, serum sodium levels were not affected except for a few days after constriction. The

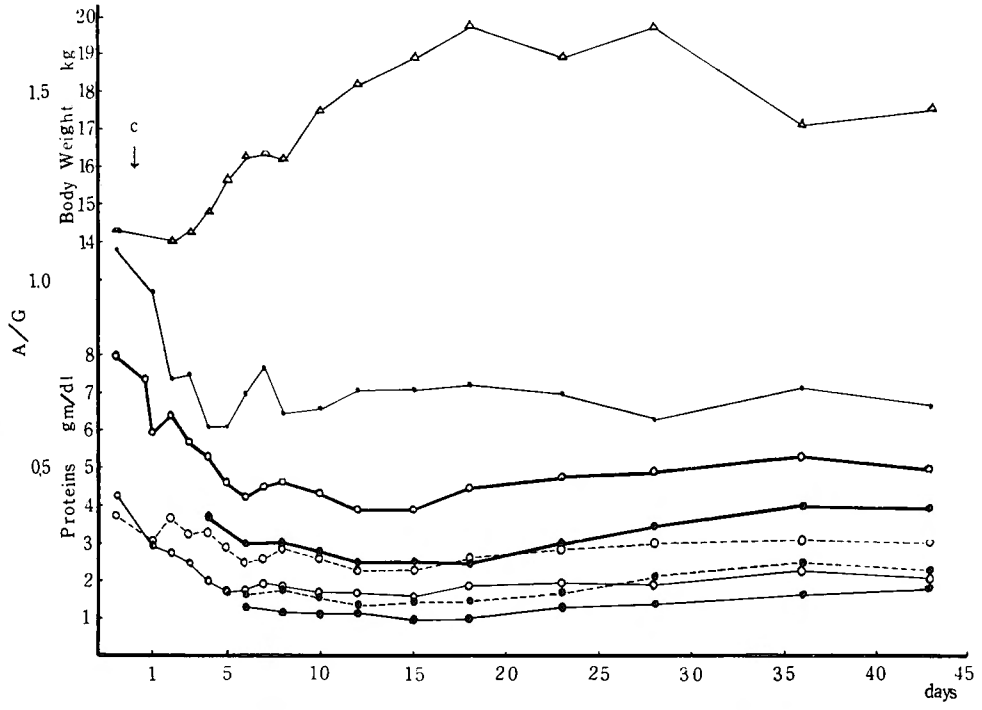


Fig. 1. Dog No. 55.

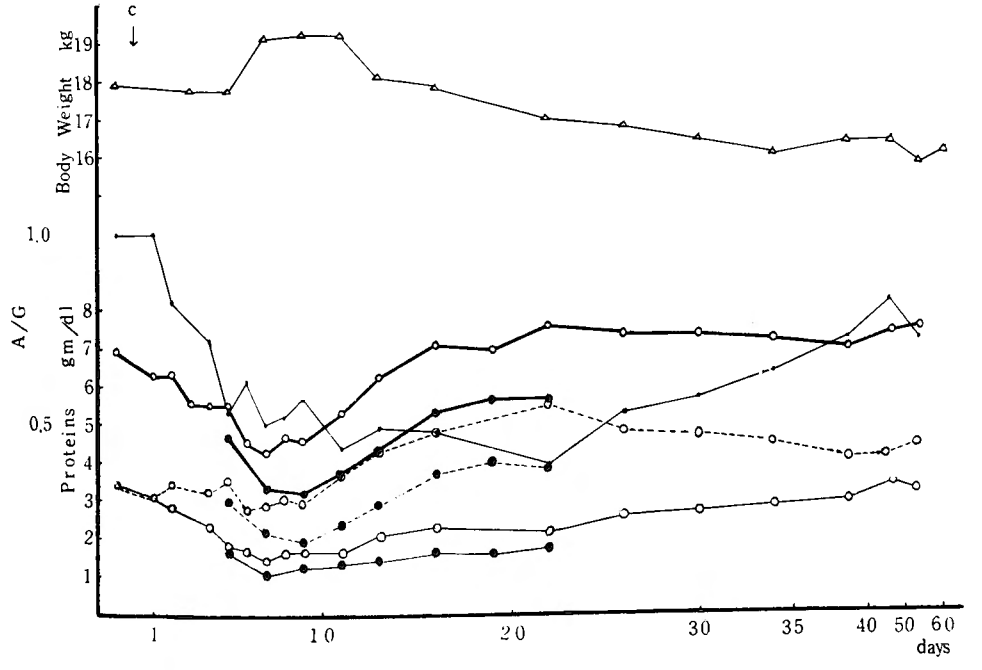


Fig. 2. Dog No. 52.

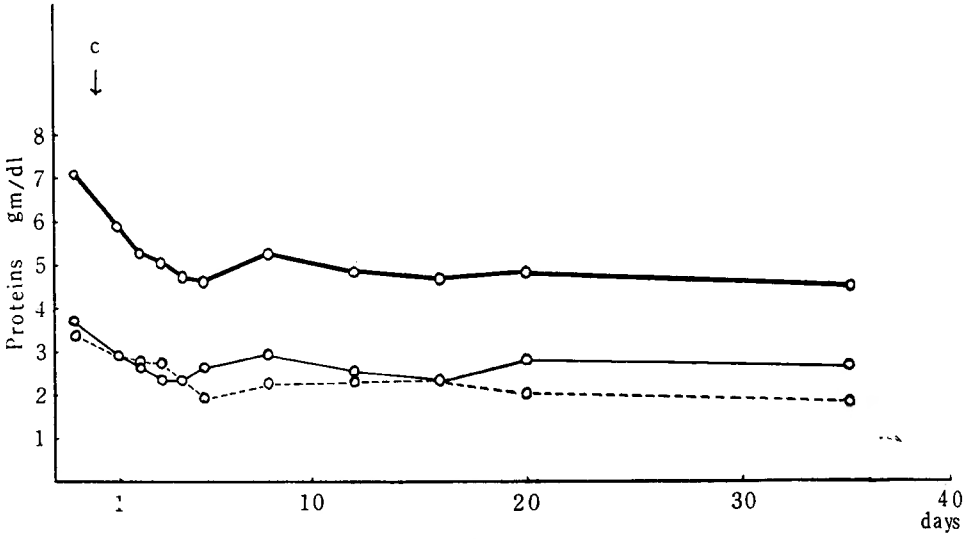


Fig. 3. Dog No. 59.

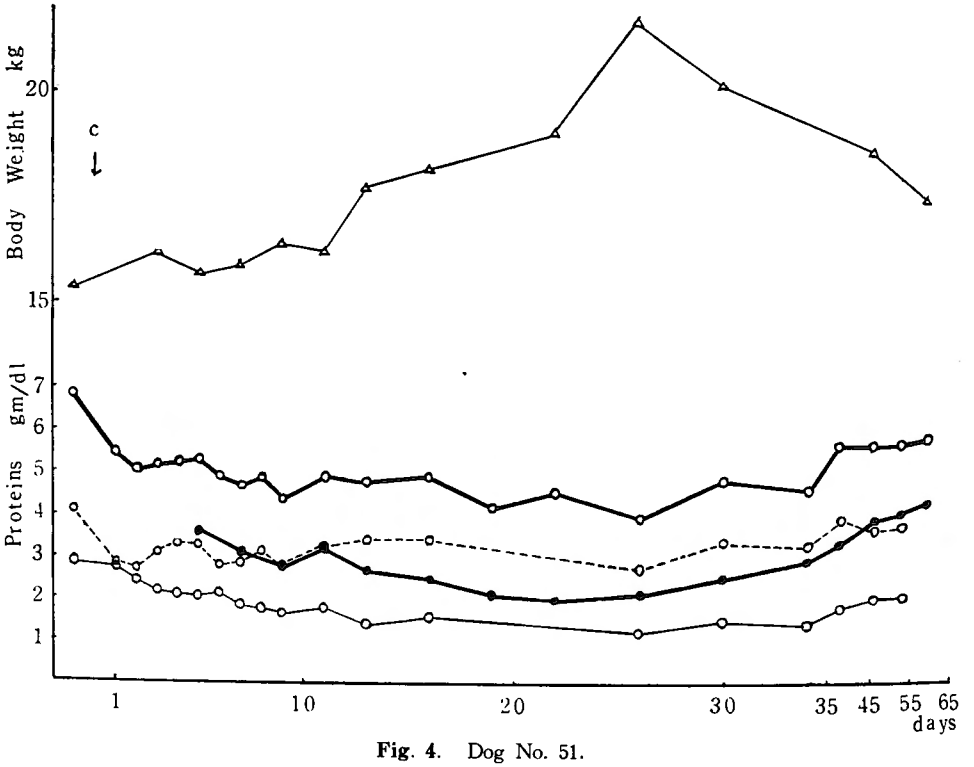


Fig. 4. Dog No. 51.

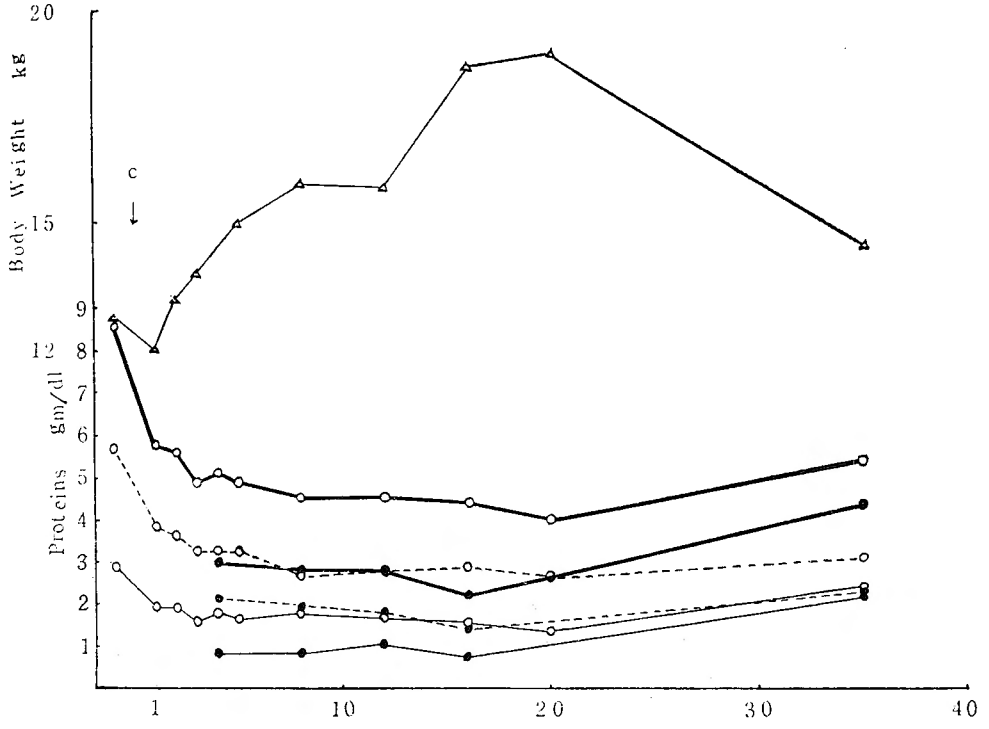
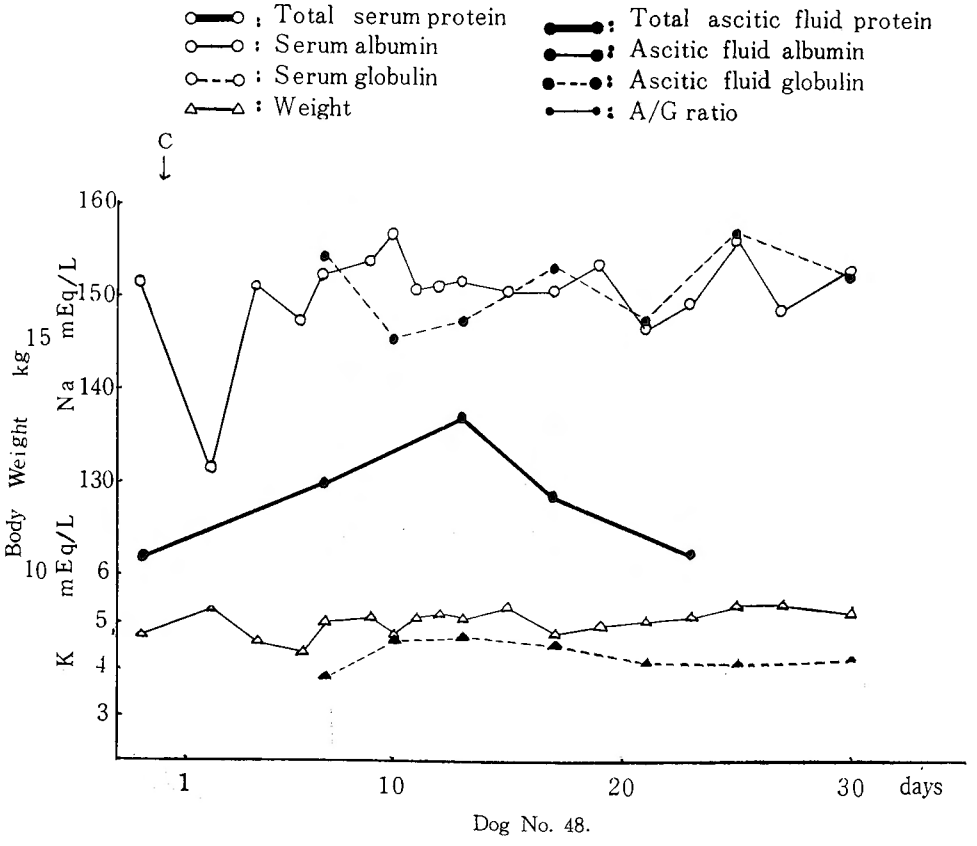


Fig. 5. Dog No. 57.

Fig. 1-5. Changes in the values for serum and ascitic fluid proteins after constriction (c) of thoracic inferior vena cava.



Dog No. 48.

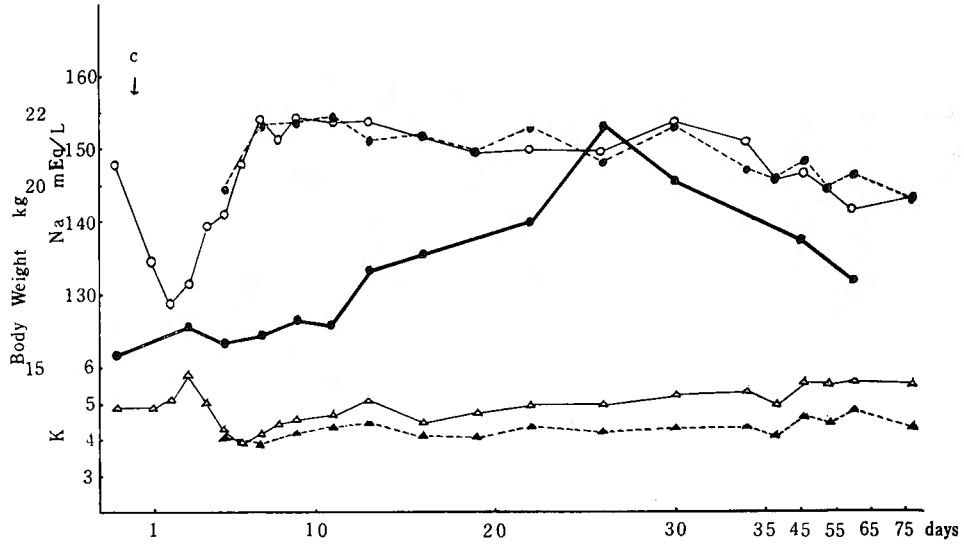


Fig. 7. Dog No. 51.

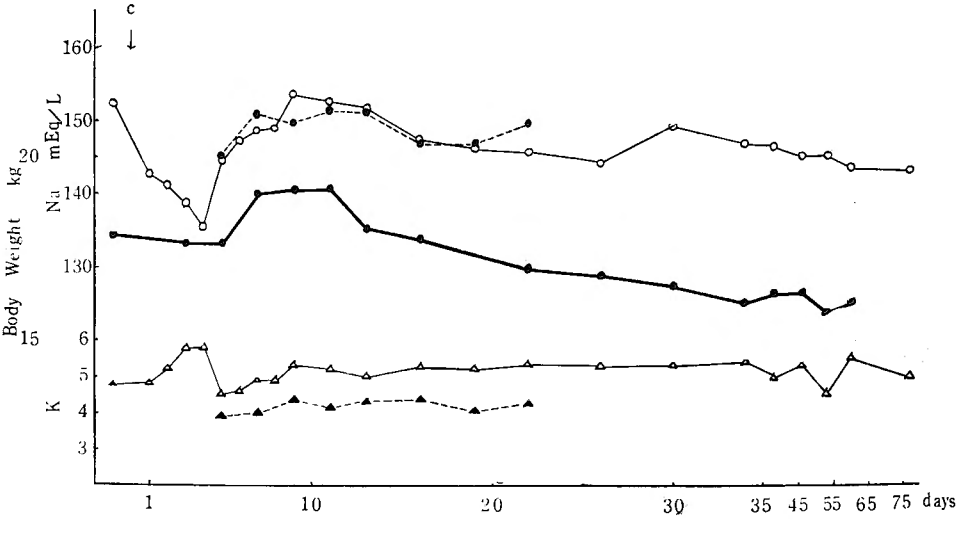


Fig. 8. Dog No. 52.

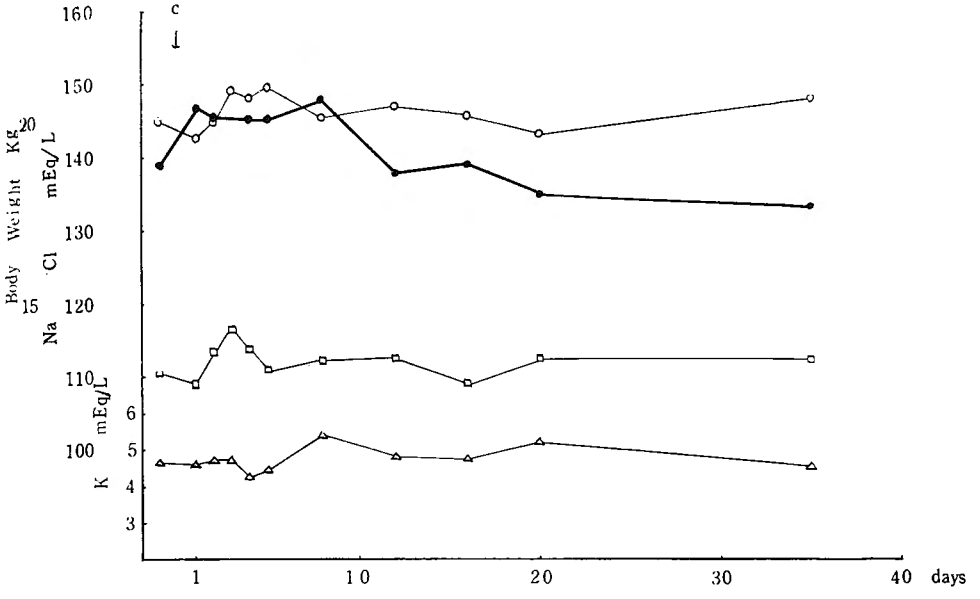


Fig. 9. Dog No. 59.

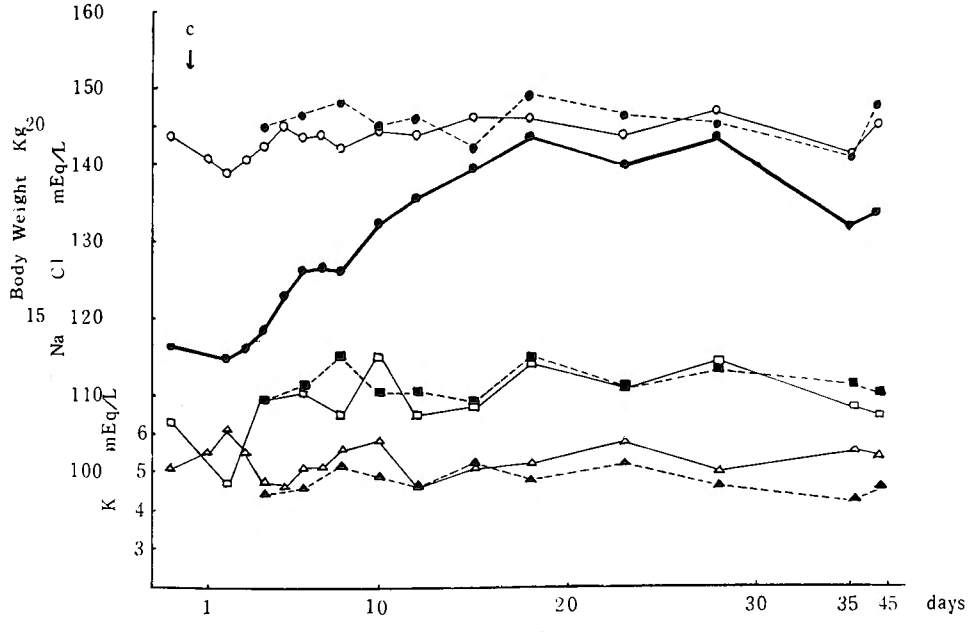


Fig. 10. Dog No. 55.

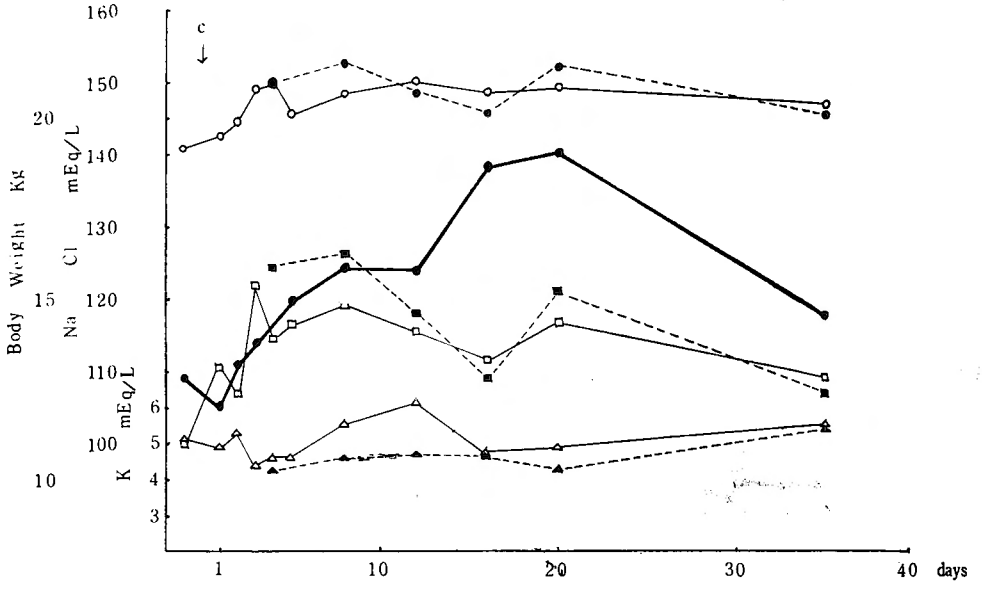


Fig. 11. Dog No. 57.

Fig. 6-11. Changes in electrolytes levels of serum and ascitic fluid after constriction (c) of thoracic inferior vena cava.

○—○ : Serum Na ●--● : Ascitic fluid Na ●—● : Weight
△—△ : Serum K ▲--▲ : Ascitic fluid K
□—□ : Serum Cl ■--■ : Ascitic fluid Cl

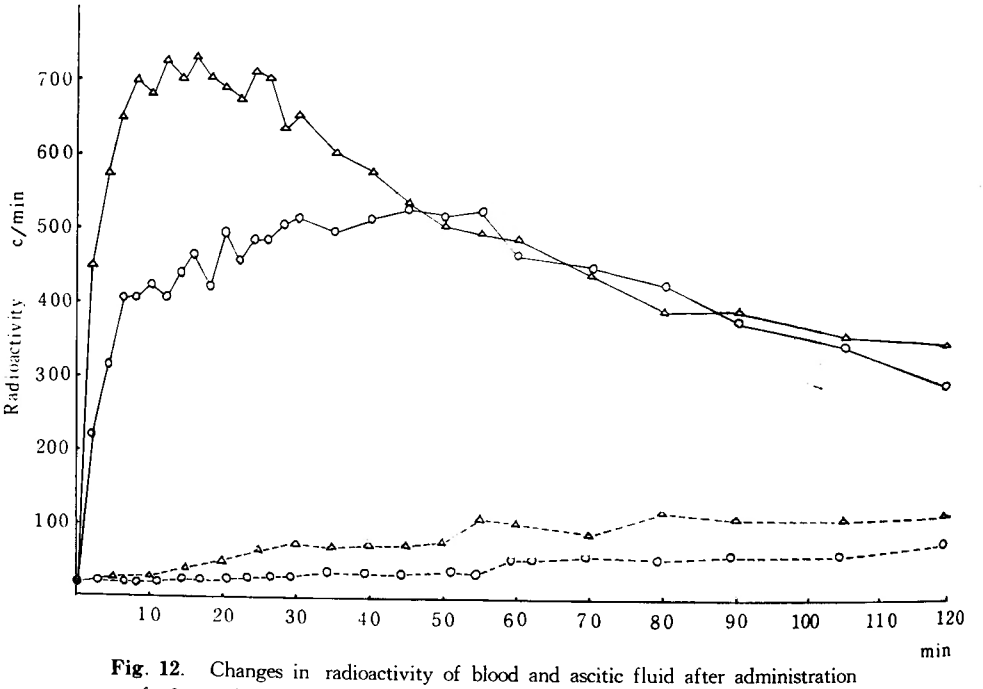


Fig. 12. Changes in radioactivity of blood and ascitic fluid after administration of p32 to the lungs

○ : Dog No. 27 —— : Blood
△ : Dog No. 40 --- : Ascitic fluid

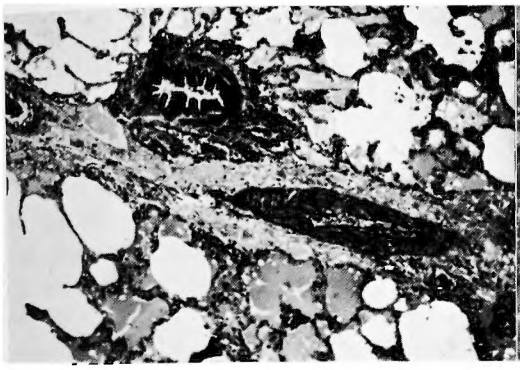


Fig. 13. Right upper lobe of dog No. 28 died on the 84th postoperative day shows transudate in the alveoli and small amount of fluid around the vessel and bronchiole. Hematoxylin and eosin stain. ×100

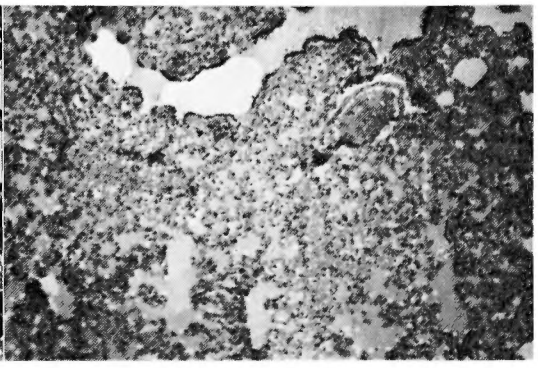


Fig. 14 Left lower lobe of dog No. 37 sacrificed on the 20th postoperative day showes large amount of transudate in the alveoli and in the bronchi. Hematoxylin and eosin stain. ×100

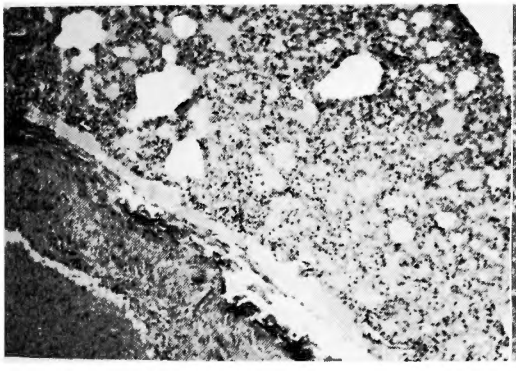


Fig. 15. Left lower lobe of dog No. 37. Transudate in the alveoli and perivascular lymphatics filled with fluid are seen. Hematoxylin and eosin stain. ×100

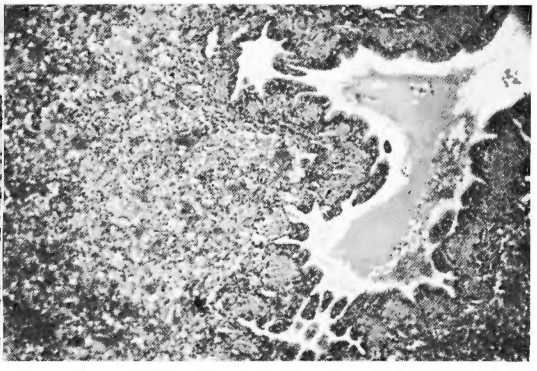


Fig. 16. Right upper lobe of dog No. 32 sacrificed on the 33rd postoperative day showes large amount of transudate and many red cells in the alveoli and in the bronchi. Hematoxylin and eosin stain. ×100

values for sodium of the ascitic fluid were similar to those of the serum.

5) Radioactivity : The rate of fluid absorption from the lungs was studied on following groups of animals ; 1) 4 normal dogs used as standards 2) 6 dogs with constriction of inferior vena cava, of which a) 4 had ascites and b) 2 had no ascites. The radioactivity levels of the blood in dog No. 27 and No. 40 were 220 and 450 c/min 2 minutes after the administration of the fluid to the lungs and to maximal values were reached 45 and 16 minutes later respectively, and then began to decrease (figure 12). There was also a gradual increase of radioactivity in the ascitic fluid. Rapid appearance of the radioactive material in the blood stream was detected in all animals.

6) The lymphatic vessels : In dogs with ascitic fluid the diaphragmatic and substernal lymph vessels were markedly dilated. Dilated efferents from edematous nodes in upper substernal portion of the chest connected the right lymphatic duct, which received the major part of the lung lymph. Connecting lymphatics between lymph vessels from the

lungs and voluminous thoracic duct were present in some cases. There were no dilated lymphatics from the lungs nor swelling of lymphnodes of both sides of the lungs.

DISCUSSION

Acute pulmonary edema may be associated with a variety of conditions, as shown by necropsy findings[18]. Experimental pulmonary edema has been induced by the use of various methods[19]. In the explanation of edema formation in the lung, Starling's law still is a good starting point. The hydrostatic and osmotic pressures of blood and interstitial fluid, are the important determinants of capillary fluid exchange.

Of six dogs with ascites, without clinical evidence of pulmonary edema, pulmonary wedge pressure was moderately increased in one, and was within a normal range in five. All but one dog showed normal pulmonary artery pressure. These results apparently indicate that the conditions produced by thoracic constriction of the inferior vena cava were not usually associated with pulmonary hypertension, which was one of the contributing elements in some cases of pulmonary edema. Luisada[20] described that it was theoretically sound to assume that pulmonary capillary pressures above 25 mmHg would lead to a transudation of plasma. However, much higher capillary pressures were required for causing pulmonary edema in experimental animals. Pressures of 30 to 40 mmHg were not unusual in patients with mitral involvement without evidence of pulmonary edema. Pulmonary edema is not necessarily associated with pulmonary hypertension.

Severe hypoproteinemia developed after narrowing of the thoracic inferior vena cava. This change occured in early stage after constriction even in dogs without the accumulation of fluid in the peritoneal cavity. The liver is the main site of synthesis of the serum proteins and is considered to be the sole source of albumin[21]. It is apparent that one of the elements causing low total serum protein and albumin levels is hepatic cell damage produced by passive congestion of the liver. Albumin largely determines the colloid osmotic pressure, since it is a smaller molecule than globulin. Therefore, hypoalbuminemia in dogs with constriction of the supradiaphragmatic inferior vena cava may be one of the important factors in pulmonary edema formation.

That the liver plays an important role in the regulation of electrolyte and water metabolism has been suspected for many decades. Eisenmenger and co-workers[22], studying 13 patients with cirrhosis and ascites, observed that there was complete cessation of ascites formation when the NaCl was limited to 1 gm per day. Higher intakes caused ascites formation in direct proportion to the NaCl given. They showed that the NaCl excretion in the urine was extremely low regardless of how much NaCl was furnished in the diet. Goodyer and associates[23] investigated renal function and salt excretion after infusion of 500 cc of 5 % saline into normal adults and into patients with cirrhosis. They found that normal subjects and cirrhotics without ascites or edema excreted a much larger amount of the administered sodium than did cirrhotics with edema and/or ascites, though the concentrations of the serum sodium rose about 10 mEq/L during the infusion in both groups. Most of the patients with cirrhosis had normal glomerular filtration rates (mannitol) and renal plasma flows (para-aminohippurate), so the results were interpreted "as evidence of a specific impairment of the renal mechanism for the excretion of administered sodium

in cirrhotics with edema and/or ascites", and as suggesting increased tubular resorption under a stimulus thus far unidentified.

Sims[24], studying 15 cirrhotic patients with ascites, found that renal plasma flow and glomerular filtration were within a normal range in 9, and moderately reduced in 6. All showed reduced sodium and chloride excretion and all but one showed increased levels of urinary antidiuretic substance. Luetscher and Johnson[25] observed significant sodium-retaining activity in extracts prepared from the urine of a number of edematous patients with lipemic nephrosis, cardiac failure and hepatic cirrhosis. They reported that amount of this activity in urine appeared to be related to the daily output of sodium, and supposed that this sodium-retaining activity in urine was attributable to aldosterone on the basis of its chromatographic and biologic properties. Davis and associates[26] showed evidence of increased aldosterone-like activity in urine from dogs with cardiac failure and from dogs with thoracic inferior vena caval constriction and observed that chromatographic fractionation and assay of extracts of urine from dogs retaining Na revealed activity in the aldosterone fraction only.

In this report, decreased sodium levels for a few days after constriction in 5 dogs were probably due to decreased sodium intake, since in one dog when high sodium chloride intake was instituted serum sodium levels were not reduced. Concentrations of serum sodium were not decreased even when accumulation of ascitic fluid was marked. The levels of sodium in ascites was as high as those of the serum. An increase in sodium-retaining hormone with accumulation of sodium and water in the body may result in ascites and/or edema and also may cause of formation of pulmonary edema.

Rapid appearance of the radioactive material in the blood stream in dogs with thoracic inferior vena caval constriction showed that alveolar-capillary transfer was not greatly altered.

Warren and Drinker[27], studying the flow of lymph from the lungs of the dog, reported that the drainage of lymph from both lungs was mainly via the right lymphatic duct, comparatively little lung lymph being delivered to the circulation by the thoracic duct. Drinker and Hardenbergh[28] showed the evidence that ANTU (alpha-naphthyl thiourea) given intravenously to dogs under nembutal anesthesia induced abnormal escape of water and plasma proteins from the pulmonary capillaries, resulting in increased lymph production and lymph flow. They described that any increase in transudate from lung capillaries, by which fluids containing the blood proteins were not absorbed except in traces[29], tended to cause pulmonary edema, since the lung lymphatics were restricted in their delivery of lymph by the small size of the right lymphatic duct. Paine and associates[30] observed that pulmonary edema was not grossly evident in the experiments where lymphatic blockage was established by cannulation of an apparently large, terminal lymph vessel. Inokuchi and Shimoo[31] assumed that it was unlikely that partial or complete obstruction of the pulmonary lymph channels might play a significant role in the development of acute pulmonary edema.

It seems likely that the presence of connecting vessels between lymphatics from the lungs and voluminous thoracic duct or the presence of dilated right lymphatic duct, which receives the major part of the lung lymph and markedly increased lymph flow from nodes in upper substernal portion of the chest, might result in increased lymphatic pressure and

restricted lymph drainage from the lungs. However, there were no dilated lymphatics from the lungs nor swelling of lymphnodes of both sides of the lungs. On microscopic examination pulmonary edema produced by ANTU showed that the lymphatic ducts were markedly distended with fluid[28)32)]. In some dogs with constriction of thoracic inferior vena cava there were small pools of fluid around the vessels with minimal dilatation of the lymph duct. Therefore, it appears that restricted lymph drainage is not on important factor in the formation of pulmonary edema.

It seems that pulmonary edema following thoracic inferior vena cava constriction is part of a diffuse anasarca which is produced by decreased colloid osmotic pressure of the blood, increased sodium-retaining hormone, increased permeability and other edematogenic factors.

SUMMARY

Macro and microscopic findings of the lungs in dogs with partial ligation of the thoracic inferior vena cava are reported. Several important factors in the production of pulmonary edema in this condition are discussed.

1) All of 12 dogs which died between the 14 th and 521 st days after constriction showed a moderate to severe degree of pulmonary edema. In 3 dogs of 10 which died within 4 days, pulmonary edema was found macro and microscopically. In 3 dogs of 7 which were sacrificed, pulmonary edema also developed.

2) Pulmonary artery wedge pressures were normal in 5 and slightly increased in 1. Main pulmonary artery pressures were also normal except 1.

3) Total serum protein and albumin levels were decreased immediately after constriction of thoracic inferior vena cava.

4) Even with marked ascites, serum sodium levels were not decreased. The values for sodium in the ascitic fluid were similar to those of the serum.

5) Rapid appearance of the radioactive material P^{32} in the blood stream was detected in all cases with thoracic inferior vena caval constriction as well as in normal dogs.

6) The presence of connecting vessels between lymphatics from the lungs and voluminous thoracic duct or the presence of dilated right lymphatic duct, which received the major part of the lung lymph and markedly increased lymph flow from nodes in upper substernal portion of the chest were observed. However, there were no dilated lymphatics from the lungs nor swelling of lymphnodes of both sides of the lungs.

ACKNOWLEDGEMENT

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和文抄録

胸部下大静脈狭窄犬に関する実験的研究

肺の病理組織学的所見及び肺水腫発生因子に関する検討

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我国における肝部下大静脈または肝静脈閉塞例のうち肺の剖検所見の記載あるもの33例につき16例に肺水腫があつたと報告されている．

実験的に胸部下大静脈狭窄犬を作り，肺の病理組織学的所見および肺水腫発生因子について検討した．

1) 肺の病理組織学的所見：狭窄後2時間～4日の間に死亡した10例のうち3例に肉眼的に肺水腫を認め，組織学的にも，これを証明した．術後13日～520日の間に死亡した犬は全例（12例）程度の差はあるが肺水腫の状態であつた．術後7日～181日の間に殺害した7例のうち3例に強い肺水腫の組織学的所見を得た．

2) Pulmonary Artery Pressureは6例中5例正常．Pulmonary Artery Wedge Pressureは6例中5例正常．他の1例は夫々やや亢進を示した．

3) 術後著明な血清蛋白の減少をきたす．腹水のたまらなかつた犬でも減小がみられた．

4) 6例中5例に術後数日間血清Na濃度の減小があり，その後増加する．他の1例は術後NaClの摂取が多かつたため，増加のみを示した．

著明な腹水増加期にも拘らず血清Na濃度の減少がなく，しかも腹水中にほぼ血清と同濃度のNaを見出した．

5) 気道内へのP^{32}注入実験では正常犬と同様，速かな血中放射能の上昇を認めた．

6) 腹水犬においては胸管拡張，横隔膜リンパ管拡張が強い．右リンパ本幹において肺からのリンパ管と横隔膜リンパをうけ，拡張した前胸壁からのリンパ管との合流を認めた．

以上のように胸部下大静脈狭窄犬においては肺水腫の合併が多くみられる．心カテーテルの結果では6例中5例が正常の肺動脈圧を示した．故に肺高血圧はこの際の水腫発生に関係がないと考えてよい．

肝鬱血のため，血清蛋白，特にアルブミンの減小があり，このため膠滲圧の低下をきたす．肺からのリンパ管と他の拡大したリンパ管との間に結合があるが，リンパ還流障害によつて肺水腫を起したとは考えがたい．

気道内P^{32}注入実験では速かな血中出現を観察したが，更に検討を要す．膠滲圧の低下，Na貯留従つて水分貯留，毛細血管の透過性亢進等によつてくる全身性浮腫の部分的な現象として肺水腫が発来するのではなかろうか．